# SUMMARY MINUTES OF THE



# GENERAL AND PLASTIC SURGERY DEVICES PANEL

# OF THE

# MEDICAL DEVICES ADVISORY COMMITTEE

## OPEN SESSION

## MARCH 1-3, 2000

**Grand Ballroom**
**Gaithersburg Holiday Inn**
**Two Montgomery Village Avenue**
**Gaithersburg, Maryland**

# GENERAL AND PLASTIC SURGERY DEVICES PANEL ROSTER

**March 1-3, 2000**

**Panel Chair**
Thomas V. Whalen, MD
Robert Wood Johnson Medical School at Camden

**Voting Members**
Joseph V. Boykin, MD
Columbia Retreat Hospital

Phyllis Chang, MD
University of Iowa College of Medicine

**Temporary Voting Members**
Karen Bandeen-Roche, PhD
Johns Hopkins University

Brent Blumenstein, PhD
American College of Surgeons Oncology Group

Boyd Burkhardt, MD
Adobe Plastic Surgery

Nancy A. Dubler, LLB
Albert Einstein College of Medicine

Stephen Li, PhD
Hospital for Special Surgery

Michael J. Morykwas, PhD
Bowman Gray School of Medicine

John A. Robinson, MD
Loyola University Medical Center

**Consumer Representative**
Maxine F. Brinkman, RN, MA
North Iowa Mercy Health Center

**Industry Representative**
Cindy Domecus
Conceptus, Inc.

**FDA Personnel**
David Krause, PhD
Panel Executive Secretary

Celia Witten, PhD, MD
Director, Division of General and Restorative Devices

Jim Dillard, MS
Acting Director, Division of General and Restorative Devices

Nancy Pluhowski
Panel Coordinator

Stephen P. Rhodes, MS
Branch Chief, Plastic and Reconstructive Surgery Devices Branch

Mr. Phil Phillips, MA
Deputy Director
Office of Device Evaluation

**OPEN SESSION—March 1, 2000**

**Panel Executive Secretary Dr. David Krause** began the Open Session at 8:10 a.m. and read appointments to temporary voting status for Drs. Bandeen-Roche, Blumenstein, Burkhardt, Dubler, Li, Morykwas, and Robinson. He also read the conflict of interest statement, noting that a waiver had been granted to Dr. Li for his interest in a firm at issue and that matters concerning Drs. Burkhardt, Chang, Li, and Morykwas had been considered but their full participation allowed. Dr. Krause also noted that guest speaker Dr. Wendie Berg, who serves as a consultant to the Radiological Devices Panel, had disclosed a previous relationship with a firm at issue.

**Dr. Thomas Whalen, Panel Chair**, stated that the charge to the panel was to make recommendations to the FDA on a premarket approval application (PMA) for a saline-filled breast implant device and that the panel members present constituted a quorum.

**SPECIAL PRESENTATION TO THE PANEL:**

**Least Burdensome Provisions of the FDA Modernization Act**

**Mr. Phil Phillips, Deputy Director of the Office of Device Evaluation,** discussed the meaning of the "least burdensome" provisions of the FDA Modernization Act (FDAMA) of 1997. He summarized these provisions as they apply to PMAs and 510ks, noting that FDAMA did not change the standard for premarket clearance and approval, which remains a demonstration of reasonable safety and efficacy or a determination of substantial equivalence to a previously cleared device. Mr. Phillips looked at FDA implementation of these provisions, saying that efforts included a January

1999 open meeting, a draft guidance document, and an industry task force. These efforts produced an interim FDA definition of "least burdensome" as a successful means of addressing a premarket issue that involves the smallest investment of time, effort, and money from the submitters and FDA. He looked at the changes that might result in FDA philosophy and discussed whether the least burdensome provisions were in conflict with scientific integrity. Mr. Phillips concluded that good science includes cost-effectiveness considerations and availability of resources and that compromise is necessary. He listed mechanisms to lessen the regulatory burden, which include reliance on nonclinical testing when possible, reliance on recognized standards, alternatives to randomized controlled trials, and use of surrogate endpoints. He concluded that the FDA remains open-minded to alternative proposals for satisfying regulatory requirements.

**Mr. Stephen P. Rhodes, Branch Chief of the Plastic and Reconstructive Devices Branch,** welcomed all participants, noting that this was the first FDA panel to make recommendations on the approvability of any saline-filled breast implant. Mr. Rhodes stated that there would be public comment at several points throughout the session, but asked participants to restrict their comments to saline-inflatable implants and not to discuss silicone-filled implants.

**Panel Executive Secretary Dr. Krause** asked all participants to disclose any travel reimbursement, financial ties to companies, societies, or industries, involvement in lawsuits involving breast implants, or income derived from surgical procedures or related complaints.

## OPEN PUBLIC COMMENT

### Individual Speakers

**Ms. Kristine Kitchen** spoke in support of saline-filled breast implants, citing her lack of problems with implants placed some 20 years ago to correct a breast deformity. She asked the panel to recommend approval of the devices in order to keep them on the market and to notify providers and patients of potential risks and benefits.

**Ms. Patricia Faussett** spoke against approval of saline-filled breast implants until long-term research has been completed. She cited her negative reactions of vision impairment, tiredness, and autoimmune problems after implants, all of which subsided after implant removal.

**Dr. Kathleen A. Melez** presented material on foreign body reactions to breast implants. She spoke against approval of saline-filled breast implants, saying they were unsafe and should not be licensed, on the basis of her experiences as a breast cancer and implant survivor who later developed foreign body reactions to the implants.

**Ms. Jennifer Gardner** spoke in favor of approval of saline-filled implants, citing her experience of having saline-filled prostheses implanted during breast reconstruction surgery following breast cancer. She spoke of the positive effect on her self-esteem and sexuality and the importance of restoring a sense of normality to cancer survivors.

**Dr. Tanya Aya Atagi of the Washington University School of Medicine** described her research using standardized instruments to assess pre and post-operative psychological traits of implant recipients. She cited evidence that the implants are durable and provide psychosocial benefits and concluded that it is important to keep the implants as an option while research efforts continue to reduce risks.

**Dr. Norman Anderson**, an internist and former panel chair, cited his concerns over the long-term survival of the implant, the degradation of the silicone shell, and the failure rate of the device over time, especially at the fold lines. He stated that the implant has the potential to achieve the highest failure rates of any device presented to the FDA over time, and he expressed his concern over PMA approval for devices that may rupture over time and might conceal breast cancers.

**Dr. Fritz Barton, a surgeon,** stated that he spoke on behalf of the many thousands of patients who say their implants improved their lives. He described the average patient and spoke favorably of the implant's effect on their lives.

**Dr. Gwendolyn Lewis** read testimony for three implant survivors who were too sick or poor to attend, stating that their illnesses were caused by the saline-filled implants and speaking against the approval of implants.

**Dr. Cheston Berlin, Jr.,** discussed breastfeeding with implants, stating that studies he has performed have shown no apparent secretion of either saline or silicone in breast milk and that there was no scientific evidence that implants are hazardous to infant health. In response to panel questioning, he noted that certain types of surgical incisions might interfere with actual ability to breastfeed.

**Ms. Melinda Cloud** discussed her negative experiences with implant surgery, saying that it was not a favor to allow women to have implants that imperiled health and could lead to destitution. She asked the panel not to recommend saline-filled implants for approval.

**Dr. Howard Ory** made a presentation on breast implants and connective tissue disease, stating that three blue-ribbon panels had found no link between silicone gel and

connective disease and concluded that breast implants do not cause connective tissue disease.

**Ms. Patricia Brent**, a mother who breastfed after receiving saline/silicone-filled implants. Ms Brent discussed her child, who has suffered from inflammatory disease and digestive disorders, and voiced her concerns on behalf of mothers who breastfed after implants and stated that the implants do cause tissue disease in the parent and feeding problems in the children.

**Ms. Ann Peterson Angus** spoke against approval of saline-filled breast implants, citing her negative experience with capsular contracture.

**Ms. Maura McGinn**, a breast cancer survivor and implant recipient, stated that manufacturers must be required to do research to ensure safety and said that the decision should be left to women unless there is incontrovertible evidence to the contrary.

**Ms. Karen Duhala** spoke in favor of allowing saline-filled breast implants to remain on the market, describing her own positive experience with a saline-filled implant.

**Ms. Lisa LaCivita** spoke as a consumer advocate for women's choice to have the implantation of a saline-filled breast implant if they so desire.

**Consumer Groups and Consumer Information Providers**

**Ms. Nicole Cummings of Implantinfo.com** described her web site and read stories from women who described their experiences with breast implants, largely but not exclusively positive. She stated that because of the Internet, women are now better informed about what the issues are.

**Ms. Anne Lowder of the Toxic Discovery Network, Inc.** described her own negative experience with saline-filled breast implants and stated that informed choice is

the key to making decisions about implant surgery, which is an elective one. She quoted another member of the network as saying that the right to choose is meaningless without the right to know.

**Ms. Lynda Roth of the Coalition of Silicone Survivors** listed the risks of saline-filled breast implants to cancer survivors, such as more difficult cancer screening and possible immuno-suppression. She stated that the manufacturer-supported studies are not impartial and have only tracked results for five years. She asked that information about saline-filled breast implants be written by those who are not breast implant manufacturers and that this information be distributed by all breast implant providers.

**Ms. Eileen Swanson of Survivors of Salines**, a cancer survivor and breast implant recipient, described her negative experience with saline-filled implants and requested denial of approval for the PMA. She stated that the standard allergy testing had not been done, that a registry of implanted women is needed, and that studies and testing should be done on implanted women who have become ill.

**Ms. Susan Sherr of the National Coalition of Cancer Survivors (NCCS)** spoke as a personal cancer survivor and on behalf of the coalition. She stated the NCCS position is that evidence-based science should be the determinant in any panel review. She stated that women do not need excessive protection from the FDA and have the right to choose a breast implant if the data that support safety are available.

**Ms. Sybil Niden Goldrich of the Command Trust Network, Inc.** stressed the need for all available data, noting that some of the data in the PMAs to be reviewed by the Panel do not support the safety of the implants. She listed four bioethical issues involving the threshold of safety and effectiveness for cosmetic surgery, the failure rate,

and the rate of complications such as capsular contracture, numbness, and infection. She stated that the patient's interest is the only valid interest in the equation.

**Ms. Cynthia Pearson of the National Women's Health Network** stated that saline-filled implants have not yet been tested adequately because there are no long-term, post-five-year data on breakage, complication, contracture, and reoperation rates, as well as post-mastectomy effects. She expressed a concern about the loss to follow-up rate, saying that the data may be flawed because of a selective bias. She felt that approval without long-term data is a betrayal of the trust women have in the FDA.

**Mr. Ron Haden of the National Silicone/Saline Implant Foundation** expressed his concern that the FDA is already biased to approve the PMAs because the saline-filled breast implants fill a perceived medical need. He hoped that the FDA would protect the consumer and not approve a device until safety and efficacy have been proved. He was particularly concerned with device failure and reoperation rates.

**Ms. Margaret S. Volpe of Y-ME** a cancer survivor and implant recipient, stated that each woman must choose for herself and noted that the availability of saline implants is very important to breast cancer survivors to give them reconstructive options. She stressed the importance of peer support and education for cancer survivors.

**Ms. Anne Stansell of the United Silicone Survivors of the World** stated that the implants are not medically necessary or life-saving devices and that the FDA should have warned women about possible dangers. She charged the FDA to validate the clinical trials before approval of the PMAs.

**Dr. C. Lin Puckett of the American Society of Plastic Surgeons** reviewed the history of breast implant surgery. He summarized major studies and findings from the

Institute of Medicine, which he saw as reassuring in not finding a linkage to autoimmune or connective tissue disease and as confirming the high level of satisfaction most patients have with their breast implants. He discussed the risks of deflation and capsular contracture and stated that there was no evidence that implants either cause cancer or conceal it from early detection. Dr. Puckett stated that women should have the right to choose whether they wish to have breast implants or not.

**Consumer Representative Ms. Maxine Brinkman** read a statement for **Elizabeth Mullen of the Women's Information Network against Breast Cancer.** The statement described Ms. Mullen's personal story and advocated women's right to choose whether they wish to have breast implants.

**Dr. David Sarwer of the American Society for Aesthetic Plastic Surgery** stated that the vast majority of implant recipients are well-adjusted candidates for surgery and will experience significant psychological benefits from the breast implant surgery.

**Mr. Pierre Blais of Chemically Associated Neurological Disorders** presented material on his study of 250 explanted devices. He stated that he felt that the implant design was flawed and that many of the implants he looked at became infected or septic. He indicated that he felt the engineering behind the valve and plug design was faulty. He also stated that breastfeeding would be difficult if not impossible with most breast implant designs and that the radio-opaque shell can generate false positives and negatives in mammography.

**Additional Individual Speakers**

**Ms. Diane Griffith** asked why the panel is considering a PMA in which the

failure rate of the shell does not meet an acceptable safety standard. She stated that the labeling does not provide information on the duration of the shell's integrity.

**Dr. Anne Caspar** discussed women's perceptions of safety of breast implants, noting that availability and safety of breast implants affect post-mastectomy choices. Most women do not know that breast implants have not been FDA approved. She stated that few would have chosen mastectomies without the implant being available because reconstructive choices are limited. She felt that breast reconstruction should remain a choice for those with cancer, but noted that the device has not been shown to be safe and effective for women who have had cancer and should not be approved until studies show such safety and efficacy for women with cancer.

**Ms. Carol Sherman** described her very positive experience with a breast implant after mastectomy and stated she was grateful that she had the option of an implant. She stated that she was informed of all risks and benefits and felt she had returned to normalcy after implant surgery.

## SPECIAL PRESENTATIONS TO THE PANEL:

### Regulation of Saline-filled Breast Prostheses:

**Dr. Celia Witten, Director of the Division of General and Restorative Devices**, introduced the discussion on regulation of saline-filled breast prostheses. She reviewed the regulatory history of these devices up to the call for premarket approval applications for saline-filled breast prostheses in August 1999. She noted that the guidance document provides manufacturers with suggested information in the areas of chemistry, toxicology, mechanical testing, and clinical data. It suggests that the clinical

study include an adequate sample size to determine a reasonably precise adverse event rate, with a separate augmentation and reconstruction cohort. Follow-up should last a minimum of two years premarket with 10 years' total follow-up. The guidance document suggests follow-up intervals, with a consideration of quality of life and a screening for connective tissue disease.

Dr. Witten stated that current studies have found no or at most a small increased risk of connective tissue disease, but these findings are based on heterogeneous studies. Local complications are not insignificant and vary widely. A key report from the Institute of Medicine (IOM) stated that local complications are the primary issue and noted a deficiency in the literature on product-specific information.

**Considerations on Imaging Patients with Breast Implants:**

**Dr. Wendie A. Berg, a consultant to the Radiological Devices Panel,** gave a presentation on imaging patients with breast implants. She noted that of the two million women with implants, 200,000 (10%) would get cancer. She discussed mammography with implants and gave survival rates over various categories. Dr. Berg stated that there is no increased risk of breast cancer resulting from the implant itself, but it is more difficult to get an accurate image of the breast with an implant. One consideration in mammography is that obtaining the best possible view can involve the use of a double radiation dose with each mammogram because there is a reduction in the visualized breast with implants. Other mammographic issues include the fact that implants can hide breast tissue directly, that adequate compression can be limited because of contracture, that lesions can be difficult to visualize with implants, and that scarring and residual calcifications can mimic cancer.

Dr. Berg stated that for her the overwhelming question is whether diagnosis of breast cancer can be delayed in women with implants. She noted there are only small studies with minimal data, most of which are on silicone-filled implants, but results of these studies may be generalizable to saline-filled implants since silicone-filled implants are more radiopaque and represent a worst-case situation. In the studies the majority of patients had only routine mammograms without displacement. More cancers were palpable at diagnosis than in nonaugmented women, but the stage distribution and survival were not different from nonaugmented women. Overall 66 percent of cancers were visible, but the performance of mammography screening is not adequately evaluated in the study.

Dr. Berg noted that other imaging methods, such as ultrasound, also have limitations. She indicated that MRI has higher sensitivity but is expensive and difficult to perform while nuclear imaging techniques are not very sensitive, but are still very expensive. She concluded that there are limitations to normal x-ray mammography for patients with implants, but there are really no good alternatives.

## OPEN COMMITTEE DISCUSSION--PMA 990075 FOR MENTOR CORPORATION'S SALINE-FILLED AND SPECTRUM SALINE-FILLED BREAST IMPLANTS

### Sponsor Presentation

**Anthony Gette, CEO of Mentor Corporation,** introduced the presenters of the PMA.

**Bobby Purkait** gave an overview of the preclinical data and described the device and its schematics. He noted that a great deal of preclinical testing was performed using state-of-the-art methods. Potential extractables were identified and quantified and were found to be at levels below toxicological concerns. Device materials were found to be stable and nonbiodegradable. He stated that a thorough battery of biological testing documented no toxicity issues, and devices and materials survived mechanical stress testing that exceeds clinical use conditions.

**Pamela Powell** read the indications for use of the Mentor saline-filled prostheses. She described the design of the clinical studies, which included two prospective studies, a three-year and a large simple trial, and three retrospective studies. Ms. Powell gave the timeline of all the studies and gave details on the two prospective study designs. She described the indications, objectives, data collection, and follow-up of the Large Simple Trial (LST), which involved 2,347 subjects. On the three-year trial, involving 1,680 subjects, Ms. Powell outlined primary and secondary safety and effectiveness objectives, data collection and follow-up, site distribution, and demographic information on augmentation and reconstruction patients.

**Dr. Bruce Cunningham of the University of Minnesota** presented the clinical safety findings. He characterized and quantified the clinical risks defined by the Large Simple Trial (LST) and other clinical data in the areas of systemic disease, local complications, durability, and cancer detection and treatment issues. Dr. Cunningham presented results from three scientific review boards, the Institute of Medicine, the National Science Panel, and the U.K. Independent Review Group on systemic disease and breast-feeding. He evaluated the safety endpoints of the large simple trial and

summarized its findings on infection, capsular contracture, and deflation. On the Saline Prospective Study (SPS), Dr. Cunningham evaluated the safety endpoints and described statistical methods used. He showed the breakdown of the different clinical populations with different clinical objectives and different complication rates.

Dr. Cunningham also demonstrated the method and extent of physician and patient information and education on infection, capsular contracture, and deflation. He placed the clinical risks in perspective with the medical literature for similar devices and indications, using long-term data from the ten-year Cunningham retrospective study where available. He also discussed incidence of reoperation and explantation among augmentation and reconstruction patients.

On cancer detection, Dr. Cunningham looked at three clinical issues of implant interference with mammography, delay of cancer detection, and compromise of clinical outcome and presented data from the SPS study and population-based research. Dr. Cunningham discussed additional statistical analyses on factors contributing to deflation and factors for breast and nipple sensitivity.

Dr. Cunningham concluded that the study data effectively define and quantify the clinical risks and local complications and that physicians and patients are fully informed about those factors. He stated that risks are consistent with those reported in the medical literature for similar devices and indications and that augmentation patients have a low risk. Reconstruction patients have higher risks but greater potential emotional and physical benefits. Revision patients have experienced similar or somewhat higher complication rates than surgery for primary implants. He noted that population-based

studies have shown that breast implants do not delay detection or compromise treatment of breast cancer.

**Dr. Rebecca Anderson of the Medical College of Wisconsin in Milwaukee** discussed device effectiveness. She described the need for the device and listed the primary and secondary objectives of the SPS as evaluation of change in breast size and of patient satisfaction and quality of life outcomes. These were assessed in augmentation patients by measuring increase in bra cup size and breast circumference and by assessing satisfaction with breast attributes and comfort and satisfaction with breast appearance. In reconstruction patients the objectives were assessed in terms of increased chest circumference and increased physical and psychological adjustment and decreased depression. She concluded that the SPS and the professional literature demonstrate that the risks and benefits are well defined and documented and that patients report high levels of satisfaction and improved quality of life despite possible complications.

**Mr. Purkait** concluded that the preclinical toxicological and durability/performance assessment had documented safety of the device. The sponsor's clinical studies document the safety and effectiveness of the devices and establish long-term durability by 10-year follow-up data. He stated that the risks were well characterized and that the device improves the quality of patients' lives and is accompanied by information and education materials for both patients and physicians.

Questions from panel members focused on fatigue testing, Betadine washing procedures, complication and reoperation rates, and the difficulty of teasing out individual practice issues versus device issues.

**FDA Presentation**

**Dr. David Berkowitz** introduced the FDA review team and described the six styles of the saline-filled and five styles of the Spectrum saline-filled devices. He read the indications for use and listed the chemical and toxicology tests, all of which have been completed. Mechanical testing is incomplete because the data are insufficient for all the styles listed in the PMA. Dr. Berkowitz also summarized the medical device reports received from 1997 to 1999 on Mentor devices.

**Dr. Sahar M. Dawisha** gave the FDA clinical overview of the device, summarizing the clinical studies. These included the Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute, the Large Simple Trial (LST), the Saline Prospective Study (SPS), and the Mentor Retrospective Study. The SEER study was a retrospective questionnaire of explant prevalence in the breast cancer population cohort. The LST was a prospective study of 3,000 to 5,000 patients with one-year follow-up to consider safety endpoints such as infection, rupture, deflation, capsular contracture, and reoperation. Dr. Dawisha gave those results by patient and summarized the implant styles studied. The SPS study was an open-label, prospective study of 1200-1500 patients with three-year follow-up to consider safety endpoints such as local complications and effectiveness endpoints such as breast dimensions, patient satisfaction, and quality of life measures. It also considered connective tissue disease (CTD), reproduction/lactation at baseline, and breast cancer/breast conditions. Dr. Dawisha showed cumulative three-year complication rates, reoperative procedures, reasons for implant removal and three-year cumulative complication rates after replacement for this study.

The SPS included a subgroup analysis on infection, capsular contracture, deflation, reoperation, and removal, which showed higher rates of complication with particular valves or Betadine. Dr. Dawisha also presented other safety information and effectiveness results from the SPS. This information showed the cumulative risk of first complication increases with time and has not leveled off. The cumulative reoperation and removal rates also have not leveled off over time. The largest reason for reoperations in augmentation patients are implant removal and due to complication rather than patient request.

**Ms. Phyllis Silverman of the FDA Division of Biostatistics** gave the statistical review, noting that the statistical sections of the PMA are comprehensive and address nearly all the questions requested in FDA's saline-filled breast implant draft guidance document. Her comments were focused on the SPS because it utilizes the devices in question, includes all of the endpoints, and fulfills the recommended follow-up. She noted that complication rates, implant survival curves, and effectiveness parameters must be evaluated from a clinical perspective. Her role was to evaluate the validity of the data rather than to judge the acceptability of the rates.

Ms. Silverman noted that statistical power was not an issue and that the sample size was determined by the desired precision of complication rates. Precision was measured by 95% confidence intervals, and the precision met FDA guidelines. She discussed Kaplan-Meier curves and presented three-year Kaplan Meier estimates for primary safety endpoints. She concluded that the data are comprehensive and the analyses consistent with guidelines. Possible biases such as nonrespondent bias, recall bias, or investigator/site bias were acknowledged. She stated that complication-free rates

are important for prospective patients and presented Kaplan-Meier estimates of such rates for augmentation and reconstruction patients at one year, two years, and three years. She noted that complications are frequent, with 57% of augmentation patients complication-free at three years as opposed to only 27% of reconstruction patients.

**Panelists Reviews**

**Panel Mechanical Review—Dr. Li**

Dr. Li's review focused on the possibilities for device mechanical failure. He agreed with the FDA that all incomplete tests must be completed, and he added that data are needed on all models and materials to be marketed. When the material to be used are tested, the gamma sterilization or other sterilization methods used must be noted. Fatigue testing shows a high variation in results and should be reanalyzed. The method of device insertion should be addressed in testing to determine the effect of load factors. Studies should focus on why and where deflation happens and on whether reverse diffusion occurs. Leakage should be addressed, as should the reason the device fails more in reconstruction patients than in augmentation patients. Dr. Li also noted that the reoperation rate is very high.

**Panel Clinical Review—Dr. Burkhardt**

Dr. Burkhardt stated that the reports of systemic illness and second-generation effects are largely anecdotal, and that the greatest concern for these implants is local complications. A major problem is the failure at fold flaws, with internal abrasion at the end of the folds. Other local complications include capsular contracture, low-grade bacterial infections, rippling, and mammography. He thought that fungal growth in saline is no longer the issue it once was because of modern filling methods, and that

mammography may be made more difficult, but does not seem to be a major issue in the outcome.

**Panel Statistical Review—Dr. Blumenstein**

Dr. Blumenstein thanked the FDA for its presentation of the data. He stated that the Cox regression analysis is useful but difficult for the patient to understand, and he recommended a covariate analysis should be included. He noted several methodological issues: the trials were not randomized and controlled, and there were no control groups. He listed a number of data issues related to informative censoring, observing that there was no analysis to characterize patients not followed at significant time points. He recommended some alternative presentation of the relative risks be given to the patients in a more understandable form.

During the following Panel discussion, the Industry Representative asked Dr. Li what the company should do to provide more mechanical testing information. It was suggested that the company should continue the retrieval analysis.

**Panel Discussion of FDA Questions**

The panel concluded that the fatigue and fold flaw testing, at best, were incomplete because not all models and materials were tested, and the fatigue and fold flaw testing performed has little or no correlation with the long-term clinical actualities.

For augmentation patients, the panel was nearly unanimous that the device is effective within the important constraints of the definition of effectiveness. There was less agreement on safety, with panel members expressing some concern about the complication rate but offering differing interpretations of that as related to safety.

For reconstruction patients, the panel noted that the effectiveness results as regards the indications are different in this subset in that this group has different options and also, the sponsor had not sufficiently assessed quality of life.

A slight majority of the panel felt that additional data should be collected in regards to the outcomes of the revision patients. There was an even split within the panel on whether to include the data already collected on revision patients as a separate cohort in the labeling or to combine those patients with the reconstruction patients.

The panel agreed that long-term follow-up for 10 years with active visits would be informative but might not be a realistic goal. All complications discussed should be tracked until they have reached a plateau as well as any other complications identified during the follow-up period. Panel members did not feel collectively that any of these concerns had to be evaluated by sponsors prior to approval.

Guidelines for surgical practice and postoperative follow-up such as not inserting the device via a long tube through the umbilicus and not using Betadine washing were suggested.

## ADDITIONAL OPEN PUBLIC COMMENT

**Lale Goddard,** who had no financial ties but was a plaintiff to a pending law suit, discussed particulate wear debris generated from implanted medical devices and requested that the panel not recommend approval of breast implants without requiring testing for cellular responses to silicone elastomer particulates. Manufacturers should also inform doctors and patients about cellular responses to silicone elastomer shell particles and cytokine production.

**Rosmary Locke, of the DOD Military Hospital Beneficiaries,** a 15-year breast cancer survivor, noted that the saline-filled implants are the only unrestricted option left to breast cancer reconstruction patients. She asked the panel to listen to the IOM recommendations, to use sound science and reasonable endpoints, and not to restrict saline-filled implants.

**Dr. Diana Zuckerman of the National Center for Policy Research for Women and Minorities** stated that she was concerned about the loss of patients to follow-up and suggested that the information dismissed as purely anecdotal might be from women lost to follow-up. She thought the quality of the data reduces the credibility of the report, noting that of the 17 studies quoted in the IOM report only one looked at saline breast implants separately. Noting the wide range of views on approval or disapproval of the implants, she stated she was not in favor of approval unless the devices were proven safe.

**Jill McClure, whose expenses were paid by the National Alliance of Breast Cancer Organizations,** said that her comments would be restricted to the availability of saline-filled breast implants for reconstructive use only and that her group does not comment on the cosmetic use of these implants. Saying that saline implants are not ideal, she expressed a hope that the FDA would look at silicone implants again but that in the meantime safe saline implants must be made available to keep options open for women undergoing reconstructive surgery. The final decision to use implants is up to the woman and the medical team.

Dr. Whalen thanked all presenters and speakers.

## FINAL REMARKS, PANEL RECOMMENDATIONS AND VOTE

The FDA had no additional comments. The sponsor stated that the data presented showed the complication rate is not increasing over time, citing the SPS study in particular.

### Panel Recommendations and Vote

Dr. Krause read the instructions to the panel. A motion was made, seconded, and passed to recommend the device for approval subject to conditions. The following conditions were unanimously approved:

1) That there be additional *in vitro* mechanical testing in cooperation with the FDA to address the engineering concerns raised in discussion (complete testing of all models and materials intended for sale in sterilization conditions, information on shelf aging, description of fatigue testing results to show what, where, when, and how devices fail, further testing to validate clinical results, and further analysis of retrievals done in serum to mimic *in vivo* testing).
2) That the comments regarding the shaped implant in promotional material and labeling be revised because there is no evidence regarding its more anatomical shape.
3) That the labeling should discourage peri-umbilical insertion.
4) That there should be collection of additional revision data.
5) That risk estimates using true cumulative incidence be reported in a way that will be more informative to the patient.
6) That a reanalysis should be done on characteristics of patients dropping out and included in the labeling and that labeling data should be presented in a way consistent with peer-reviewed journals.

7) That long-term follow-up data be collected on patients potentially part of an informative censoring pattern.

8) That the quality of life data on revision patients be dropped from the labeling.

9) That sponsors and the FDA work on the protocol for reasonable assurance that patients will be accurately and reasonably informed of all risks.

The motion to recommend the PMA as approvable subject to the foregoing conditions was passed with one dissenting vote.

Dr. Witten thanked all presenters, sponsors, and panel members.

The meeting was adjourned for the day at 9:30 p.m.

## OPEN SESSION—MARCH 2, 2000

The meeting was called to order at 8:10 a.m. **Dr. David Krause, Panel Executive Secretary**, read appointments to temporary voting status for Drs. Bandeen-Roche, Blumenstein, Burkhardt, Li, Morykwas, and Robinson, and Ms. Dubler. Dr. Krause also read the conflict of interest statement, noting that waivers had been granted for Drs. Li, Burkhardt, Chang, and Morykwas for their past and present interests in firms at issue and their full participation allowed.

**Panel Chair Dr. Thomas Whalen** noted that the panel would be discussing two premarket approval applications and noted that the voting members present constituted a quorum. He asked the panel members to introduce themselves.

**Dr. Celia Witten, Director of the Division of General and Restorative Devices,** provided follow-up to three topics from the previous day's session. She noted that the 180-day review period begins from the date the PMA is filed. Dr. Witten also reminded the panel that each PMA must stand on its own.

## OPEN PUBLIC COMMENT

**Ms. Liz McCloud** related her own unsuccessful experience with a saline-filled breast implant that ruptured, suggesting that the panel give greater weight to considerations of local pain, capsular contracture, and informed consent procedures.

**Dr. Leroy Young of the Plastic Surgery Educational Foundation** analyzed capsular contracture, deflation issues, failure rates, and reasons for reoperations. He stated that saline-filled implants are safe and produce high satisfaction rates, with a complication rate of 1-4%. He suggested the need for a better informed consent form, a

device registry, analysis of retrieved devices, more research, better definition of the problem, and a device forum. In answer to questions from the panel, he recommended that a registry be maintained by organizations of plastic surgeons.

## OPEN COMMITTEE DISCUSSION--PMA P990074 FOR MCGHAN MEDICAL'S RTV SALINE-FILLED BREAST IMPLANT

### Sponsor Presentation

**Dr. Scott Eschbach, president and CEO,** described the company and introduced the sponsor team.

**Dr. Raymond Duhamel** discussed preclinical studies and testing. He stated that all elements of the FDA guidance on preclinical testing had been addressed, and 15 of the 17 test areas are complete. Discussions continue with the FDA on fatigue and fold flaw testing. He presented rupture rates, stating that the largest cause of device failure is fold flaw, but the cause of the folds is still undetermined.

Dr. Duhamel also gave an overview of the four prospective multi-center studies, the AR90, the LST, the A95, and the R95, noting that the latter two are ongoing. He discussed patient enrollment, demographics, device style, and incidence of breast cancer in the implant population. He presented information on connective tissue disease and local complications and explained the methodology used to collect these statistics.

**Dr. Scott Spear** discussed implant removal and replacement, noting that for augmentation patients the primary reasons for removal were size and style, leakage, and capsular contracture. For revision patients the reasons for removal were capsular contracture, leakage, and deflation. Secondary reasons for surgery are usually procedure-

related complications. He stated that the incidence rates nonetheless supported reasonable risk/benefit ratios.

**Dr. Marie Pletsch** presented effectiveness data for the sponsors, saying there was no doubt about the efficacy results. She discussed quality of life concepts such as physical health, emotional health, self-esteem, and satisfaction. She concluded that the device has an excellent risk/benefit ratio, reflecting the high satisfaction rates and relatively low complication rates.

**Dr. Duhamel** concluded the sponsor presentation with a brief review of the device benefits.

Questions from the panel to the sponsors concerned valve failure, fold flaws, connective tissue disease (CTD), missing follow-up data on quality of life, effect on breast-feeding, safety, and pain data.

**FDA Presentation**

**Dr. Sam Arepalli** introduced the FDA review team, described the device, and read the proposed indications for use. He presented preclinical testing information on chemical and toxicology tests, which were complete. Mechanical testing was complete except for fatigue rupture and fold flaw tests. He also summarized Medical Device Reports on the McGhan device.

**Dr. Sahar Dawisha** gave the clinical overview. She summarized the five clinical studies: the Surveillance Epidemiology and End Results (SEER) Program of the National Cancer Institute, the Large Simple Trial (LST), the Augmentation and Reconstruction 1990 study (AR90), the Augmentation Study of 1995 (A95), and the Reconstruction Study of 1995 (R95). She summarized the SEER study, noting that the main reason for

saline breast implant removal in this retrospective questionnaire of explant prevalence in the breast cancer population was capsular contracture. She also described the LST study design, which was a safety only study of 3,000-5,000 patients with one-year follow-up and presented the Kaplan-Meier results for infection, deflation, and capsular contracture rates. Dr. Dawisha described the AR90, which was an open label, prospective study with five-year follow-up of 300 patients, and showed patient disposition at five years as well as intra-operative medications and by-patient five-year cumulative Kaplan-Meier complication rates. The AR90 study also provided information on type of reoperation procedure and reason for implant removal through five years, as well as other safety information. A subgroup analysis on augmentation patients showed a statistically higher leakage/deflation for leaf valve and submuscular placement and a numerically higher infection, removal, and capsular contracture for the leaf valve, which has since been removed from the market. Effectiveness results showed increased bra and cup sizes, satisfied ratings and generally improved quality of life measures.

Dr. Dawisha described the study design of the A95 and R95 studies and showed the patient disposition at three years for both. She presented the by-patient cumulative four-year Kaplan-Meier complication rates and the type of reoperation procedure, as well as the reason for implant removal through four years and the two-year cumulative complication rates after replacement for the studies. A subgroup analysis again showed higher leakage/deflation rates and implant removal rates for the leaf valve. Other safety information from the study found no changes in reproductive or lactation problems, no increased breast disease in reconstruction patients, and a slight increase in breast disease for augmentation patients. She analyzed new reports of CTD and analyzed effectiveness

results in the AR95 study. Dr. Dawisha concluded that the cumulative risk of first complication increases with time and has not leveled off and that there is a cumulative four-year reoperation rate of 24% and a removal rate of 10% for augmentation patients. The largest cause of reoperations in augmentation patients is implant removal due to complications. The breast size benefits were evident for augmentation patients, with quality of life benefits less apparent. Quality of life generally improved for reconstruction patients.

**Dr. Telba Irony** gave the statistical analysis of the AR90, A95 and R 95 studies, noting there were no claims, targets, or control groups in the studies, only descriptive statistics to describe safety and effectiveness endpoints. Sample sizes were previously determined to achieve precision for the estimates as defined by the length of the confidence intervals for the adverse event rates. The targeted precision was achieved. She described the statistical techniques employed to assess safety, noting that the estimates are very sensitive to biases generated by loss to follow-up. Quality of life measurements were appropriate, but statistically significant change in breast or cup size was meaningless because the breasts were physically enlarged during the surgery. She noted possible biases of nonresponse, recall, and investigator/site. Other analyses that could have been performed included using demographic variables as covariates, checking the correlation among adverse events, combining the augmentation studies from 1990 and 1995 and looking at the statistically significant differences between these studies.

**Panelists Reviews**

**Panel Mechanical Review—Dr. Li**

Dr. Li was impressed with the sponsors' testing approach but expressed concern over relating that data to clinical performance. He thought the fatigue testing deficient and was unclear what the fold flaw data meant. He stated that he was unclear why sponsors picked the tests they did and how to interpret the information they provided.

**Panel Clinical Review—Dr. Boykin**

Dr. Boykin expressed a significant level of comfort with the clinical data, saying that the overall studies show some consistency and the present device with the diaphragm valve design shows some improvement (less leakage) over the previous model with the leaf valve. He was comfortable with leakage and deflation rates and stated that the cumulative rates, although biased, is what is generally seen. He raised three points: whether there was a replacement policy for the leaf valve versus the diaphragm design, what measurement issues on quality of life measures should be considered, and how differences in shape should be addressed in product labeling.

**Panel Statistical Review—Dr. Blumenstein**

Dr. Blumenstein noted his concern about informative censoring in the data, saying there was no characterization or analysis to show the percentage of informative censoring. He thought the statistical analysis should have been performed as cumulative incidence rates. Prevalence estimates as presented should be dropped. A proportional hazard regression approach would have been better. He suggested that the characterization of risk should be redone to sharpen the characterization between normal

surgical complications/adverse events/device problems/surgeon mistakes. In conclusion he stated that the method of presentation could be improved.

**Panel Discussion of FDA Questions**

The panel recommended that fatigue testing is important and should be standardized with sponsor-FDA concurrence. Fold flaw testing may not be as important as previously thought in assessing long-term rupture or leakage.

There was a panel consensus that the device is reasonably safe and effective in both augmentation and reconstruction patients, with some editorial caveats on how efficacy as studied and designed might not be as good as they could have been. Safety analysis should distinguish between complications specific to implants and normal surgical complications that occur with many surgeries. More data on the cohort of revision patients would be useful but should not be a condition for approval.

The majority of the panel thought that a 10-year follow-up period was the best duration, with a minority saying that five years would be sufficient. Active follow-up is preferred, with passive follow-up as a backup position. Complications as defined in the LST should be followed.

The panel was unanimous in stating that sponsors did not need to provide evaluation on interference with screening mammography or lactation or effects on offspring as a condition for approval. They stated that these are, however, important issues that should be included in the device informed consent form and labeling and on which it is desirable to accumulate data.

There was a general concern expressed by the panel regarding the need to improve educational process for physicians. Another concern among panel members

involved the factors inherent in complications regarding positions and insertions rather than the device itself.

## ADDITIONAL OPEN PUBLIC COMMENT

**Dr. Patricia Lieberman of the National Center for Policy Research** expressed her concerns over the safety of this device and the one approved the previous day.

**Dr. Harold J. Brandon of Washington University** gave an analysis of breast implants from the Washington University Implant Retrieval Program. He described the breast implant inventory of more than 500 explants and explained the research objectives. He noted that strength could vary by implant type. He presented data from failure analysis, noting that failure tends to occur in folds rather than with large-scale shell degradation.

**Dr. Wendy Anne Epstein,** a patient with Mentor implants, recommended that women have a baseline mammogram before implantation and have submuscular implantation to prevent mammographic interference. Saline implants provide greater radiolucency and thus are better. Although submuscular implantation requires general anesthesia and nerve damage remains a possibility, there is less possibility of damage to offspring or interference with breast-feeding.

## FINAL COMMENTS, PANEL RECOMMENDATIONS AND VOTE

The Agency had no additional remarks. The sponsor thanked the FDA reviewers and the panel.

The Consumer Representative addressed a remark to sponsors and the panel asking for responsible promotion and marketing, with no ads targeted to teenage girls. She noted that ads have no references to possible side effects.

**Panel Recommendations and Vote**

Dr. Krause read the panel voting options. A motion was made, seconded, and passed to approve with conditions. Those conditions are the following:

1) The revision category should be dropped and the two categories of augmentation and reconstruction should be considered as the indications.
2) Changes should be made in the labeling and marketing materials to eliminate references regarding the proposed anatomical advantages of the device pending studies suggesting reasonable scientific evidence that such is the case.
3) Long-term active follow-up should focus on active censoring, with the FDA and sponsor to determine an appropriate length.
4) The risk characterization analysis should be redone with appropriate characterization of complications versus adverse events.
5) An analysis should be provided on censoring and quality of life data to characterize the sample and as representative of the general population.
6) Discrepancies between the CTD data presented by the PMA, the FDA, and other speakers should be clarified.
7) Mechanical testing should include testing on the thinist wall and the highest potential for failure. Sponsors should work with the FDA on acceptable fatigue and fold flaw testing.

8) A standard operating procedure should be completed and followed for looking at explants and to tabulate the model and wall thickness of these devices.

The motion was passed unanimously.

## OPEN PUBLIC COMMENT

**Dr. James L. Baker, Jr. of the Aesthetic Surgery Education and Research Foundation** described the benefits and the psychological issues involved in breast augmentation. He stated that the benefits are real and outweigh the risks and described detailed psychological studies of psychosexual aspects of breast augmentation.

## OPEN COMMITTEE DISCUSSION—PMA990077 POLY IMPLANT PROTHESES USA (PIP)

### Sponsor Presentation

**Dr. Rick Hawk** described the history of the company and the device itself, noting it was a prefilled device with no valve. He defined valid scientific evidence and listed a U.S. and a French prospective study and a U.S. surgeon case survey as part of that evidence. He listed the preclinical testing done on cytotoxicity, sensitization, irritation, intracutaneous reactivity, and acute systemic toxicity.

**Dr. George Burdock** presented the preclinical data from the tests listed above. He concluded that the elastomer is biocompatible and that all *in vitro* and *in vivo* studies were negative. All findings were also congruent with the literature such as the IOM report and peer-reviewed published literature.

**Dr. Ionana G. Carabin** discussed complications from implantation such as deflation and capsular contracture and presented clinical data from the U.S. clinical study, the U.S. surgeon case experience survey, and the two-year French clinical study. She listed indications and contraindications for the device, types of surgical incisions and placement, and types of implant, along with follow-up through October of 1999.

Dr. Carabin presented safety/effectiveness data on capsular contracture, displacement, folds, deflation, change in nipple sensitivity, asymmetry, pain, and inflammation for both the augmentation and revision cohorts with various implants and placements. She noted in particular that there was 0% incidence of capsular contracture grade iii and iv for texture implants placed rectopectorally or subglandularly.

Dr. Carabin also presented material on connective tissue disease and complications, noting that most of the complications in the cohorts were rare. Changes in nipple sensitivity and asymmetry were more common, but were still within the range of reported incidences in the literature. Quality-of-life data was assessed with self-reported quality-of-life scales. Data on increase in cup size were also presented.

Dr. Carabin provided data about the U.S. surgeon case experience survey on 35,000 implants in the United States, some of whom are two or more years postoperative. This survey showed a relatively low rate of complications and a relatively high rate (88.5%) of patient satisfaction.

**Dr. Margan Goudeau** presented further data from the French clinical prospective study on 520 patients to evaluate the complication rate. He listed the indications for use, surgical placement and incision, and contraindications, and presented statistics on follow-up out to 24 months. Dr. Goudeau showed data on augmentation and revision cohorts for

deflation, capsular contracture, infection, folds, asymmetry, and nipple sensitivity, showing 0% autoimmune disease, pregnancy difficulty, lactation difficulty, calcification, extrusion, necrosis, pain, or hematoma at 24 months.

**Dr. Carabin** concluded by noting that 35,000 PIP prefilled saline breast implants have been marketed in the United States. Preclinical studies have shown no toxicity, and clinical data have shown low rates of complications and high rates of patient satisfaction. She also listed mechanical testing performed and briefly described the tests.

In questions to the sponsors, panel members asked how the current device differs from that presented a number of years ago. Sponsor representatives replied that the new shell was thinner and harder.

At this point, the FDA presentation was deferred so that the Open Public Hearing could be held.

## ADDITIONAL OPEN PUBLIC COMMENT

**Cynthia Pearson, National Women's Health Network**, noted that consumers would like to see what the unexpected and adverse events are and what the likelihood is, especially for longer than two years. For augmentation patients in particularly, it would be reasonable to share the global number of adverse events because these women do not plan to go back for a second procedure.

**Diana Zuckerman of the National Center for Policy Research for Women and Families** noted the public confidence in the FDA to protect health, even with problematic data. She expressed concern about the higher dropout rate and smaller

sample size in this study and asked the panel to hold to a standard that makes sense to consumers.

**Tom Hudson of Baylor College of Medicine**, whose expenses were paid by PIP, gave his results using the PIP implants and discussed how technological changes in this type of implant had minimized many common complications and side effects.

**OPEN COMMITTEE DISCUSSION (continued)**

**FDA Presentation**

**Dr. Peter Hudson** introduced the FDA review team and described the device. He listed the proposed indications for use and reviewed the preclinical chemistry, toxicology, and mechanical data, noting that many tests were still incomplete. He also listed the medical device reports received from 1997 through 1999 on the PIP device.

Dr. Hudson presented clinical information based on the U.S. surgeon case experience survey, the U.S. clinical study (the Discretionary Postmarket Surveillance or DPS), and the French Clinical Study. He described all three of these studies and summarized both their strengths and weaknesses. Strengths included relatively high numbers of augmentation patients, while weaknesses included relatively lower samples of revision patients, problems of bias, and protocol deviations or abnormalities.

**Judy Chen, M.S.,** gave the FDA statistical review of the three sponsor studies. She presented strengths and weaknesses of all three studies as well as key data from each. On the postmarketing surveillance study, she commented on the high proportion of missing data, and the fact that event time may not be independent of censor time and other adverse event times. Regarding the French study, she noted the lack of a protocol

and the likelihood of bias in results because censoring was not appropriately adjusted, missing follow up and complication data, and possible underreporting effects.

**Dr. Hudson** read the FDA questions for panel review.

**Panelist Reviews**

**Panel Mechanical Review—Dr. Li**

Dr. Li noted an incomplete device description and incomplete clinical specifications and analysis. He said that it was not clear what was being tested chemically or dimensionally. He saw no information on fold flaw or static rupture and the information on fatigue rupture testing was confusing. He cited a lack of information and rationale on loading and felt that the sponsor had not completed the testing that was specified in the FDA guidance document.

**Panel Clinical Review—Dr. Chang**

Dr. Chang noted that the clinical data are a work-in-progress, but observed that the number of patients in each of the cohorts in the prospective study is smaller than the number of patients recommended by the FDA. She felt that the deflation rates cited at two years were good but asked if data was available for the smooth implant. She recommended longer follow-up on the folds in the implant and noted a potential difficulty in fine-tuning the volume of fill, which could cause an asymmetry problem.

**Panel Statistical Review—Dr. Blumenstein**

Dr. Blumenstein stated that the use of true incidence would have been a better methodology for a later presentation. He also noted that the U.S. study is not yet complete.

In panel comments, one member noted the potential of the device for reduced leakage and greater palpability but expressed concerns regarding the lack of complete product testing. The sponsors replied that additional data clarifying the follow-up statistics were presented in a February 2000 PMA Amendment, which had not yet been reviewed by the FDA.

**FDA Questions**

The panel agreed that the carcinogenicity, toxicity, implantation, pharmacokinetics, biodegradation, and chemical tests listed are crucial and the data they provide is critical. The engineering material properties are also critical. The fatigue testing methodology used was unproven and its relevance was unknown. Further fold flaw information is critical, and there is a wealth of chemical and physical data not forthcoming from this sponsor that are essential.

The panel concluded that the U.S. DPS data are essential for the PMA, but the data as presented are not mature enough to permit an evaluation of safety and efficacy. Data from the French study cannot stand alone, and the collection of U.S. data was still in progress. The weakness of the U.S. Surgeon Case Experience Survey was well described. The data in each subset of the PMA are inadequate and do not justify an evaluation of safety and efficacy.

The panel agreed that 10-year post approval follow-up should be a minimum and the sponsor should strive for active visits, with particular attention to device failure, leakage, rupture, and asymmetry.

Consistent with its prior opinions, the panel agreed that while the issues of interference with mammography, lactation, and effects on offspring are important,

information on them is not necessary as a condition of approval. The panel also agreed that while physician training is important, it is best left to the head of the training institutions.

On the risk of asymmetry and the risk of changes in nipple sensitivity, the panel expressed concern that the data is still incomplete. If rates prove to be as high as currently noted, they should definitely be listed in the labeling and informed consent.

## FINAL COMMENTS, PANEL RECOMMENDATIONS AND VOTE

The Agency had no additional comments. The sponsor representative read a statement saying that changes in design had addressed design defects, but they would work with the FDA to answer questions and issues raised by the panel. They added their opinion that their data supported reasonable assurance of safety and efficacy and met the threshold for approval.

### Panel Recommendations and Vote

Dr. Krause read the voting options. It was moved and seconded to recommend the PMA as not approvable because the data were much too preliminary, especially in the U.S. sources. The motion passed unanimously. The panel also recommended that the sponsor address deficiencies such as information needed on smooth versus textured implants, thickness of implant, and asymmetry of results; and to provide information from a completed clinical study with adequate follow-up.

Dr. Whalen thanked the panel and all presenters and adjourned the meeting at 5:47 p.m.

## OPEN SESSION—MARCH 3, 2000

**Panel Executive Secretary David Krause** opened the session at 8:02 a.m. He read the conflict of interest statement, noting that matters concerning Drs. Burkhardt, Chang, and Morykwas had been considered and their full participation allowed. **Panel Chair Dr. Whalen** noted that the purpose of the day's session was to make recommendations to the FDA on the content, format and consistency of labeling and informed consent documents used for saline breast implants.

**Celia Witten, Director of the Division of General and Restorative Devices,** welcomed all participants, especially those from the public, to the day's session and invited their comments.

Dr. Whalen introduced the presenters from industry.

## LABELING PRESENTATIONS FROM INDUSTRY

**Scott Eshbach of McGhan Medical** described three routes for information dissemination to patients and physicians. The first is the device packaging, which includes the FDA "Information for Women" document, the informed consent document, the claims processing program data, the patient device ID card, and an information packet for the physician. The second is educational material for patients such as pamphlets on silicone and choices in breast construction and augmentation and materials for physicians such as instructional monographs and videos, wall charts, and planning tablets. The third route is web-disseminated information such as the pamphlets listed above.

McGhan's advertising philosophy involves product promotional ads with legally mandated "fair balance" of risks and benefits and reminder ads without this discussion of

risks and benefits in newspapers and magazines. Medical journals also feature physician-directed articles on product technical failures. Mr. Eshbach asked the panel to consider three points: the need for a consistent approach across industry, the need to cite actual data that are specific to the manufactured devices, and a phased-in replacement for current labeling.

**Donna Crawford of Mentor Corporation** discussed her company's approach to communications through its current programs and labeling and its proposals for new content and expanded communication methods. She listed communications channels such as a toll-free phone number staffed by nurses, educational videos, and an interactive web-site. Patient labeling contains three brochures, the FDA "Information for Women" and "Options in Breast Augmentation/Reconstruction," all of which she described. Ms. Crawford listed new initiatives to communicate new detailed clinical results on both risks and benefits via expanded web-site communication and focus groups to discern the most effective methods of communication.

## OPEN PUBLIC COMMENT

### Comments from Professional Societies

**Dr. Shawna Willey of the American College of Surgeons** focused on the principles of informed consent. She noted that patients must talk to their surgeons and discuss individualized options. She warned against unrealistic expectations regarding the duration of the device and possible complications and recommended that the FDA draft outline might serve as a checklist for surgeons to review during the informed consent process. The checklist could also be included with the information insert in the device

packaging. Good understanding of the procedure should include clear differentiation between risks and complications that have been proven and those that have not. She opposed a mandatory waiting period before device implantation on the grounds of questionable legality, practicality, and needless inconvenience.

**Dr. Mark Jewell of the American Society for Aesthetic Plastic Surgery** discussed informed consent, suggesting the most comprehensive approach possible. He thought such an approach should include a discussion of appropriate indications for surgery, description of the procedure, alternatives to implants, discussion of inherent device-specific risks and general surgical risks, and other advisory information. Such information would cover implications for mammography and pregnancy, likelihood of breast disease or autoimmune disease, long-term results, and statistics on revision, replacement, or removal. Medical risks should be related to familiar risks patients encounter in their daily lives and explained in a variety of ways. Benefits should also be discussed. Dr. Jewell did not recommend a waiting period for breast augmentation because the operation is typically scheduled far in advance in any case. He also recommended against a waiting period for reconstruction patient because decisions must be made quickly in order not to delay cancer treatment. Dr. Jewell provided the panel with copies of a their proposed informed consent documents.

**Dr. Bailey of the American Society of Plastic Surgeons** noted that informed consent is communication and is more than a legal process. He opposed a mandatory waiting period but noted that many doctors impose a waiting period in any case or refuse patients with the wrong motivations for surgery.

In answer to questions from the panel, both Drs. Bailey and Jewell stated that physicians who advertise should not be treated differently from those who do not and that advertising was not per se a conflict of interest. With respect to patient understanding of risk, Dr. Jewell thought it was possible to quantify risk in ways that were meaningful to patients.

**Comments from Individuals**

**Mary McDonough, an implant recipient** who said she thought she was making an informed decision but did not receive true informed consent, expressed her concern that saline implants are hardly a safe alternative to silicone implants and that approval with so many conditions is hardly a clear signal of safety. She recommended conducting independent research on saline implants and strengthening informed consent documents to include the absence of scientific information on breast-feeding and complication rates, the financial implications, insurability issues, and psychological aspects of surgery.

**Liz Macleod, an implant recipient,** stated she was not provided with proper informed consent and did not know the regulatory status of breast implants. She felt that patients should know about shell permeability, gel-bleeding possibilities, risk of multiple surgeries, and health complications. She would have wanted to know the regulatory status and been informed about the lack of long-term studies on failure rates and shell degradation. She noted that it is in the financial interest of manufacturers and surgeons for the devices to fail, and that labeling and informed consent are not panaceas. The burden of risk is unfairly placed on the user, and she reminded the panel of the Hippocratic Oath versus caveat emptor.

**Lisa Hickey, an implant recipient who had experienced denial of insurance coverage**, stated that both Mentor and McGhan repeatedly violated Good Manufacturing Practices and underestimated adverse events. She suggested that true long-term studies would show that breast size and patient satisfaction actually decrease over time and that many long-term problems are not reported in the database because patients do not return to their doctors. She also reminded the panel that device failure causes permanent results.

**Dr. Roberta L. Gartside, a plastic surgeon,** shared her experience of the last 11 years, listing low rates of complications. She discussed the negative media attention implants have received, saying this was upsetting and potentially misleading to women who needed to explore all reconstructive options available after mastectomy.

**Dorothy Stull, a breast cancer and reconstruction patient,** stated that she had had no problems with her saline implants, she hoped that saline-filled implants would remain an option because of the advantages to psychological self-esteem for implant recipients.

**Dr. Saul Puszkin** discussed the immunogenicity of latex and silicone and the scarring potential of both. He spoke on his lab experience and discussed the molecular structure of silicone, saying that implants must have expiration dates because the material will decay.

**Dr. Britta Ostermeyer** discussed adjuvant breast disease in patients with saline-filled implants. She gave demographics and statistics on her patients with problems with saline-filled implants, saying that women need to be aware of the risk of local injury and local response as well as systemic illness. She recommended that more long-term data be

collected and that surgeons explore patient expectations and explain potential complications, including health insurance coverage.

**Comments from Consumer Groups**

**Marlene Keeling of Chemically Associated Neurological Disorders** stated that she had received no informed consent document with her implant in 1978 and that the current document is written to escape legal liability. She recommended that a complete list of all chemical and safety data must be provided and that the product insert, FDA information, informed consent document, and video explaining complications all be presented at the initial consultation. Further recommendations were that a patient identification card with all information be given at surgery and that a statement that the FDA has not formally approved the devices should be given to the patients.

**Dr. Diana Zuckerman of the National Center for Policy Research for Women and Families** stated her concern about the gap between the oral and written informed consent procedures and her concern about insurance coverage. She stated that there is a gap between what women are told and what research shows on advice and options for breast cancer patients, and a gap between the manufacturers' understanding of their own data and the FDA understanding of it. She recommended that informed consent should include photos of what negative consequences can look like, a listing of what is and is not known on systemic disease, and the statement that implants change the body permanently.

**Martha Murdock of the National Silicone/ Saline Implant Foundation** stated that informed consent documents do not contain all the information that manufacturers have and that manufacturers do not reveal all they know. She noted that patients do not

always get the package insert and that failure rate tables should be available in all informed consent documents. She also raised the lack of health and life insurance coverage for implant recipients.

**Anne Stansell of United Silicone Survivors of the World,** a cancer survivor and implant recipient, stated her concerns about the lack of device warranty, lack of device registry, and lack of health insurance availability. She stated her concern that the FDA did not have full facts before approval and her feeling that the process of approval was flawed. She ceded her remaining time to **Marlene Keeling,** who read the denial of health insurance she had received.

**Amy Allina of the National Women's Health Network** discussed how the Network is based on the right of all women to make choices based on complete information. She stated that all available information should be in the informed consent document and should be substantiated. Complications, deflation rates, benefits, risks, and photographs of unsuccessful and successful surgeries should be covered in an easy-to read presentation.

**Rosmary Locke of the National Alliance of Breast Cancer Organizations** stated that general information on reconstruction options and devices should be included in the informed consent document. A better informed consent would help remove patients' sense of betrayal. She recommended that all clinical trial information should be included in a standardized approach. Focus testing should be done to see how people receive and retain information. Cost of revision surgery and life expectancy of the implant should be in the informed consent document. Implants should have a bar code for easier tracking, and patients should receive a full description of the operation in advance.

A device registry card and patient identification card should be included with the informed consent document.

## DISCUSSION OF BREAST PROSTHESIS LABELING

### Panelist Presentations

### Panel Discussant—Nancy N. Dubler, LLB

**Ms. Dubler** noted that the informed consent document was developed as a way to redress problems in the balance of power in the relationship between doctors and patients. The doctrine requires a decisionally capable person who is able to articulate personal values and make valid choices. Legally it is a risk management technique, not an empowerment technique. She stressed the need for a new paradigm among manufacturers, surgeons, surgical organizations, consumer organizations, patients, and partners on the principles of transparency, awareness of risk, and availability of independent sources of information. These three principles should be added to informed consent principles. Transparency requires that any data should be given to women in the most informative form possible. The FDA should highlight risk awareness with consumers in any ways possible, and the authority of the FDA should extend to promotional material. The FDA should give web-sites as independent sources of information as part of the informed consent process. Ms. Dubler added that web-sites might lack quality control but do give both sides of the information to women.

### Panel Discussant—Maxine F. Brinkman, R.N.

Ms. Brinkman stated that she had listened to dozens of consumers and groups and would share their comments with the FDA. The consensus was that informed consent

documents should be improved in content and the consent process should be improved. The challenge is in providing a nontraditional approach to getting information to consumers. Health care providers need to learn how to reach consumers better. Specific suggestions included the following. There should be improved multimedia access to information, especially improved risks and benefits information. Photographs of desirable and undesirable results should be available, and web-sites with hyperlinks should be additional resources. Detailed instructions for mammography should be given to patients, and medical costs and issues of insurance availability should be discussed in advance. Insert material should be duplicated for patients with full listing of all potential complications. A national registry of all implants with identification cards for recipients would help facilitate further information dissemination. Ms. Brinkman also noted that both manufacturers and the FDA have responsibilities in advertising, especially in terms of age limits, and that concise physician training should be available before physicians are able to purchase any product.

**FDA Presentation**

**Stephen P. Rhodes, Chief of the Plastic and Reconstructive Surgery Devices Branch,** summarized the history of the FDA in getting information to consumers on saline-filled breast implants, from the Federal Register Notices of 1991 and 1995 to the Breast Implants Consumer Handbook. He listed the elements of both Federal Register notices and the patient risk information sheet entitled "Information for Women Considering Saline-filled Breast Implants." Mr. Rhodes also described the consumer handbook, which explains the availability and regulatory status for breast implants and summarizes risk/benefit factors. The handbook also has information on special medical

and physical considerations and a section on adverse reaction reports. It lists frequently asked questions and discusses mammographic considerations. Mr. Rhodes noted that the FDA draft guidance on medical device patient labeling is still being completed.

Mr. Rhodes also presented an informed decision information template. After a brief introduction, the document includes a purpose statement, a brief background on breast surgery and description of the implants, and a discussion of indications and contraindications. It describes the breast implant surgery and summarizes clinical results, including studies, complications, and safety data. Potential risks listed include general risks, specific risks, and epidemiology on long-term risks. Additional information would include a warranty, patient assistance information, and date of printing. Mr. Rhodes concluded with five questions to the panel.

## ADDITIONAL OPEN PUBLIC COMMENT

**Dr. Kathleen Melez** spoke against advertising and suggested that studies should be lifelong. She also suggested additional studies on foreign body reactions.

**James K. Russano of Children Affected by Toxic Substances** expressed his concern over children whose mothers received implants and later breast-fed. He noted that the safety of breast-feeding and effects on health of young girls was never proven. He asked the panel to make a clear statement that no research was ever done on pregnancy and breastfeeding and that there were no data on women of childbearing age. In answer to a panel question, he stated that no women should ever have breast implants until they are proven safe.

## PANEL DELIBERATIONS AND RECOMMENDATIONS

**Mr. Rhodes** clarified that the panel's charge was to provide information on what kind of information should be offered in the patient information template and should accompany the product to explain risks and benefits. He also asked for guidance on how to present adverse events.

In general discussion, the panel recommended presenting product-specific and procedure-specific adverse events and appropriate data to show incidence in understandable form. Missing scientific evidence should be noted, and extensive data should be presented in a bulleted text with an overall summary of adverse events. One recommendation was to use actuarial estimates with some caveats on informative censoring. Current materials used in labeling should clarify the high loss-to-follow-up rate. Other surgical options should be listed and discussed in the materials. Any information provided in the physician's packaging insert should also be available to the patient before the operation. Reoperation should be listed as a risk, and patients must understand this is a lifelong commitment. Complications should be outlined, and photographs of bad results should be considered. Any potential for insurance problems should be carefully noted. Packet information should also include independent sources of information.

The FDA was strongly urged to work with surgical and medical organizations to refine the consent process and encourage outcome analysis of the consent process, and the Consumer Representative will provide the consumer input she received. Manufacturers should also analyze whether patients are receiving and understanding the

information provided. Patients should be encouraged to record their interviews with their doctors to help prevent misunderstandings.

Other comments were that a registry is important for device tracking. Preoperative mammography is a good idea and should be encouraged. Advertising should not be allowed to target teenagers.

In discussion of the panel questions, the panel recommended that discussion of cosmetic benefits in the informed consent or promotional material should include risks like asymmetry as part of the efficacy data. Psychosocial terminology should be used in discussion of risks and benefits. All statements should be backed up with careful wording, and quality-of-life data should be presented with especially great care.

There was some split on the panel regarding a suggested waiting period prior to surgery. Some suggested a one-week waiting period for augmentation surgery and no waiting for reconstructive surgery, but they did not recommend a mandated waiting time.

The panel listed postoperative symptoms requiring a physician's care as inordinate swelling, redness, drainage, signs of infection, bleeding, swelling, chills, fever, and so forth. Women should see themselves as data providers on complications, and there should be a reporting repository to facilitate data reporting. A national registry would be useful to track long-term complication rates.

What information a patient should be given regarding differences in surgical procedures should be left to the professional organizations and societies.

Additional information that could be included would be results of chemical, mechanical, or biological testing. Issues of lactation, mammography, reporting adverse events, complications, and hypo or hypersensitivity should be discussed.

The panel briefly discussed whether hospitals could require some type of physician education or credentialing before surgeons could receive hospital privileges to perform breast implant surgery. However, it was felt that such hospital regulation would be very difficult to enforce. It was noted that the FDA can ask manufacturers to have a training program available but cannot restrict availability to those who do training.

Drs. Witten and Whalen thanked the panel and all presenters. Dr Whalen assured all presenters that their tragic stories were heard and understood. He also thanked panel Executive Secretary David Krause.

The meeting was adjourned at 2:45 p.m.

I certify that I attended the Open Session of the General and Plastic Surgery Devices Panel Meeting on March 1-3, 2000, and that this summary accurately reflects what transpired.

David Krause

David Krause, Ph.D.
Executive Secretary

I approve the minutes of the meeting as recorded in this summary.

T. V. Whalen, MD

Thomas V. Whalen, M.D.
Panel Chair

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